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Back to Basics: The Effects of Buffered Crystalloids on Mortality in the Setting of Severe Trauma

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BACK TO BASICS: THE EFFECTS OF BUFFERED CRYSTALLOIDS ON MORTALITY IN THE SETTING OF SEVERE TRAUMA

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ABSTRACT:

Trauma is the leading cause of death for people between 0 and 45 years of age. An important step in the management of trauma patients is the replacement of a large volume of fluids, typically with normal saline. However, normal saline has been implicated in the development of metabolic derangements that may contribute to a large proportion of deaths in trauma patients. In this study, we will examine whether less acidic solutions that contain buffers can improve survival in trauma patients compared to normal saline. **We will perform a double-blind randomized control trial to determine whether fluid replacement with Lactated Ringer's solution or a solution of 0.45% normal saline and sodium bicarbonate in a prehospital setting can improve survival in trauma patients compared to normal saline**. The insights gleaned from this study could dramatically alter the management of trauma patients and save countless lives.

Chapter 1: Introduction

1.1 Background

Traumatic injuries are, far and away, the leading cause of death in individuals age 0 years to 45 years.[1] A common consequence of trauma is profound hypovolemia as a result of blood loss and vascular hyperpermeability.[2] In order to maintain hemodynamic stability in these patients, fluid resuscitation is often required. The most ubiquitous fluid used to resuscitate these patients is normal saline (0.9% NaCl).[3,4]

1.1.1 Acidosis in Trauma as it Relates to Fluid Resuscitation

Despite its predominance as the most utilized crystalloid in trauma patients, the use of normal saline is commonly implicated in the exacerbation and development of metabolic derangements including hyperchloremic acidosis and dilutional coagulopathies.[3,5] Normal Saline is relatively acidic (pH ~4.5-5.0) when compared to some other alternative crystalloids including Lactated Ringer's Solution (pH ~6.5).[6] In the body, large volumes of normal saline increase the concentration of unpaired chloride ions which contribute to hyperchloremic acidosis due to their strong ionic influence.[7] Trauma patients are already at high risk for developing acidosis as lactic acid accumulates quickly in the body due to poor perfusion that is associated with even relatively minor traumatic injuries. Certain traumatic injuries such as rib fractures may indirectly contribute to respiratory acidosis as a result of hypoventilation secondary to painful inspiration.[8] The acidic profile of normal saline is notable for many reasons but perhaps the most significant of which is its effects on coagulation. Previous studies have noted that coagulation factors require a relatively narrow pH range to respond appropriately.[9] This is significant in trauma patients that may have multiple bleeding

injuries contributing to their hypotension as delays to coagulation can exacerbate exsanguination and hemodynamic collapse. It has also been observed that large volumes of normal saline can contribute to systemic vasodilation, which is highly problematic in patients that require intravenous fluid to compensate for volume loss.[6]

1.1.2 Sodium Bicarbonate Solutions and Lactate Ringers

Lactated Ringers (LR) and Normal Saline (NS) are among several different crystalloids that are considered for fluid resuscitation. Another less common approach to fluid resuscitation involves the dilution of sodium bicarbonate in 0.45% NaCl to create a sodium bicarbonate solution (SBS). One study by Hashemi et al described the process of mixing this solution by adding three 50 ml vials of NaHCO3 solution into 850 mL of 0.45% NaCl (1/2 NS) solution to get to a final concentration of 1.3% sodium bicarbonate solution[10]. In order to achieve this final concentration, 8.4% bicarb vials would be required. The purpose of this custom solution was to better account for physiological changes in pH and osmolarity associated with blood loss in the context of surgical hemorrhage. In the aforementioned small study (n=66) hemodynamic stability was observed more in the SBS group when compared to LR. One benefit of this custom solution is its hypertonicity compared to lactated ringer's which is relatively hypotonic (272 mOsm/L)[6]. Lactated ringer's low osmolarity/tonicity makes it a controversial choice for patients with traumatic brain injury as a hypotonic solution may increase intracranial pressure as a result of diffusion; however, this link has not been established definitively.[11]

There is significant reason to believe that Lactated Ringer's or sodium bicarbonate solutions may be better choices for fluid resuscitation in trauma patients. While the electrolyte profile of LR is not identical to that of plasma, it more closely

resembles the ion composition of plasma than normal saline, and the concentration of chloride in LR mirrors physiologic chloride levels, reducing the concern for hyperchloremic acidosis[6]. Some data also suggest that lactate may be a preferred energy source in states characterized by ischemia, including trauma[12]. Perhaps the most significant benefit of lactate is its ability to be metabolized into weakly basic bicarbonate ions in the liver that can correct acidosis[13]. As mentioned earlier SBS is hypertonic and may be safer in patients with traumatic brain injury to limit edema. It also contributes more to alkalization than LR. One liter of lactated ringer's contains 130 mEq of lactate which is converted 1:1 to bicarbonate[13]. SBS contains 150 ml of 8.4% sodium bicarbonate which contains 1 mEq of bicarbonate/mL, increasing the availability of bicarbonate ions by ~15% compared to LR (130 mEq vs 150 mEq). SBS also has the benefit of not requiring metabolism from lactate to bicarbonate, as some research suggests that lactate metabolism may be impaired in critical illness due to the oxygen-dependent nature of the acetate and lactate metabolism pathways[7].

1.1.3 Notable Findings of Past Studies

For a myriad of physiological reasons, there is significant reason to believe that either of the solutions mentioned above may incur a mortality benefit when compared to normal saline. One RCT attempted to simulate traumatic blood loss by evaluating healthy patients following blood donation. These patients were randomized to a no-fluid group, Lactated Ringer's, or normal saline. The results of this RCT show that patients receiving normal saline had a statistically significantly lower blood pH than those that did not receive replacement fluids or those that received LR, supporting the idea that normal saline can contribute to acidosis. The same paper also demonstrated statistically

significant increases in serum levels of bicarbonate in the LR group compared to the no fluid or NS group.[7]

The study that was the most similar to the study that will be proposed here was a randomized controlled trial conducted by Young et al that compared normal saline to an isotonic crystalloid called Plasma-Lyte A, using the mean change in base excess as its primary outcome. Once again, this study demonstrated that the administration of a balanced crystalloid solution was associated with more favorable metabolic profiles when compared to normal saline, including acid-base balance and chloride levels[14].

1.2 Statement of the Problem

The prevalence of traumatic injuries and the metabolic complications associated with normal saline has led many researchers and clinicians to posit that a different fluid should replace normal saline as the standard of care in these patients. While these theories have been proposed there has not yet been a randomized controlled trial that has evaluated mortality as a primary outcome when comparing normal saline to lactated ringer's or SBS.

1.3 Goals and Objectives

The study will allow us to determine if there is a difference in in-hospital mortality in trauma patients that receive normal saline compared to those that receive SBS or LR as the primary outcome. Secondary outcomes will include the need for intubation, blood products, length of hospital stay, and length of intubation (when required). The goals of the study are to fill the gaps in the literature that are described above. In addition to the novel study design, this will be the first study that begins the intervention in the field. Previously mentioned studies such as Young et al began the

fluid intervention on arrival to the hospital after EMS had already administered their fluids. By randomizing the fluid selection in the field and carrying that fluid through initial stabilization in the hospital, there will be continuity of the intervention from the time that the treatment is initiated. Not only will early intervention contribute to the continuity of management, but it will also, theoretically, allow for the early accumulation of bicarbonate before acidosis begins to develop[5].

Randomized Controlled Trials are uncommon in trauma management because of the difficulty in obtaining informed consent from patients that are incapacitated or otherwise disoriented following trauma. In order to conduct this research, we plan to utilize the FDA's exception for informed consent (EFIC) that allows for a subject's enrollment in a study before consent can be obtained in cases where an intervention is required urgently, as is the case with fluid resuscitation in trauma patients.[15,16]

1.4 Hypothesis

We hypothesize that trauma patients with an injury severity score (ISS) of 16 or greater that receive normal saline as their primary resuscitative fluid will have significantly higher rates of mortality compared to those that receive Lactated Ringer's or the Sodium Bicarbonate Solution. We expect patients that receive LR or SBS to have in-hospital mortality rates that are approximately 14% lower than those that receive NS.

1.5 Definitions

1. Lactated Ringer's is an intravenous fluid used for volume resuscitation that contains sodium, chloride, potassium, calcium, and lactate. This solution will be used as one of the three arms in this study.

2. Normal Saline (also known as 0.9% sodium chloride) is an intravenous fluid used for volume resuscitation that contains sodium and chloride. This solution will be used as one of the three arms in this study.

3. Sodium Bicarbonate is a well-known buffer that will be added to 0.45% sodium chloride (otherwise known as "half normal saline") to create the sodium bicarbonate solution that will be used for volume resuscitation as one of the arms of this study.

4. Injury Severity Score is a scale utilized to assess the severity of a patient's traumatic injuries. The scale considers injuries to different anatomical regions and ranges from 1-75, with scores of 16 or more being considered "severe".

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Chapter 2: Review of the Literature

2.1 Introduction

A systematic literature review was performed on the following databases: PubMed, Cochrane, Scopus, and Embase. The literature search was performed in December of 2020 using the keywords Normal Saline, Sodium Bicarbonate, Lactated Ringers, Trauma, and Metabolic Acidosis. Synonyms for normal saline included “0.9% saline”, and “0.9% NaCl”. Synonyms for sodium bicarbonate included “carbonic acid monosodium salt”, “sodium hydrogen carbonate”, and “baking soda”. Synonyms for Lactated Ringers included “lactate, ringer's”, “Hartmann’s solution”, “lactated ringer’s solution”, and “ringers lactate”. Synonyms for trauma included “injuries and wounds”, “research-related injuries”, “injuries”, “wounds”, “hemorrhagic shock”, “traumatic brain injury”, “cerebrovascular trauma”, “head injuries, penetrating”, “war-related injuries”, “head injuries, closed”, “hypovolemic shock” and “burns”. Synonyms for metabolic acidosis included “acidosis”. Due to the limited number of randomized controlled trials and human studies, the literature search includes animal research and observational studies. Review articles were utilized to describe important physiological concepts. The articles included in the literature review were published no earlier than 2011. Only articles that were available in English were included.

2.2 Complications Associated with Trauma

Trauma is the leading cause of death between the ages of 0 and 45 years in the United States. [1] The worldwide burden of death due to trauma is staggering. In 2010 there were 5.1 million deaths due to injuries which accounted for nearly one out of every 10 deaths. [2] Despite continual advances in safety and technology in the automotive and

medical industries, the rate of deaths that occur within minutes following trauma has remained relatively static over the last several decades, at around 50%.[3] The purpose of this study is to evaluate the management of trauma patients that survive past this "immediate death" window, many of which go on to develop severe metabolic complications that can result in life-threatening complications such as hemorrhage and multiorgan system failure.

The pathology of complications associated with trauma is complex and it would be impossible to describe all of the physiological responses that may occur following trauma in the scope of this study, however, it is important to recognize several of the most notable derangements and how standard interventions may influence, and exacerbate those derangements. Despite the ubiquity of traumatic injury, there are very few studies that have attempted to describe the physiology of multi-system injury or hemorrhage in humans due to practical and ethical considerations. For this reason, many of the metabolic responses that are theorized in humans have been observed in animal models.

2.2.1 Acidosis

Perhaps the most significant and notable physiological response to trauma in the context of this study is the development of metabolic acidosis. The cause of this acidosis is cellular hypoperfusion, the etiology of which is multifactorial. [4-6] One such reason for decreased blood supply to end organs is obvious; many trauma patients suffer from hemorrhage. As total blood volume decreases, perfusion suffers. Further exacerbating hemorrhage, there are documented physiological changes at the cellular and molecular level that can hinder coagulation. One such complication observed in rats with traumatic

brain injury (TBI) is the inhibition of the adenosine diphosphate and arachidonic acid pathways that are mediators of platelet aggregation, an important step in the formation of blood clots that could otherwise stop, or slow bleeding. [4] Another significant mediator of poor perfusion is vasoconstriction. During physical trauma, there is a significant sympathetic nervous system response, mediated by the release of endogenous catecholamines. These catecholamines have several physiologically beneficial effects in trauma such as helping to maintain mean arterial blood pressure (MAP) through inotropic effects on the heart and an increase in systemic vascular resistance (SVR), however, this increase in SVR is achieved through vasoconstriction.[7] On their own a decrease in blood volume or vasoconstriction can reduce end-organ perfusion. Many patients suffering from trauma-related injuries have both. As tissues receive less blood flow, they become hypoxic and must convert from aerobic cellular metabolism to anaerobic metabolism. [5,6] Byproducts of this anaerobic metabolism are ultimately converted into compounds that contribute to metabolic acidosis.[8] A study by Raffee et al identified that several coagulation markers including prothrombin time (PT) and partial thromboplastin time (PTT) were elevated in patients that had arterial blood gas suggestive of acidemia. [6] This finding suggests that there is potential for a dangerous cycle of hemorrhage leading to acidosis leading to decreased coagulability and, consequently, worsening hemorrhage. Furthermore, a study by Epstein et al found that patients with isolated traumatic brain injury had significantly greater mortality when they had an elevated INR ($\geq$ 1.3) compared to those with a normal INR (45.1% vs 12%, $p < 0.01$), indicating that acidosis could incur other coagulopathy-related mortality risks beyond those associated with hemorrhagic shock.[9]

Beyond the known physiological effects of acidemia on patients suffering from traumatic injury, several studies indicate that acidosis identified via arterial or venous blood levels are significant predictors of trauma-related death. A study by Shane et al found that a statistically significant number of patients with low pH (< 7.32) or low bicarbonate (<21 mmol) died as a result of secondary organ failure (p=.04 and p=.02 respectively).[10] The early appropriate care (EAC) protocol is a system used to categorize patients into low-risk or high-risk groups of developing complications or succumbing to their injuries.[11,12] EAC stratifies risk through blood levels of three markers associated with acid-base balance. For a patient to be stratified into the high-risk group patients must meet all three criteria (pH <7.25, Base excess <-5.5, Lactate $\geq$4).[11] A study by Halvachizadeh et al found that EAC has a statistically significant predictive capability in terms of death from multiorgan failure (OR 2.1, p-value .04) and death within 72 hours (OR 1.5, p-value <0.001) when comparing high-risk groups from low-risk groups.[12] Gale et al also note that initial lactate levels are correlated with outcome.[13]

2.2.2 Other Complications Associated with Trauma

While acidosis is an important complication with several systemic ramifications it is not the only physiological response that plays a role in the outcomes of trauma patients. Exsanguination due to traumatic hemorrhage can result in hypothermia which has been implicated in coagulopathies. [14-18] It should also be noted that hemodilution on its own does not appear to account for the coagulopathic effects seen in hypothermic trauma patients.[15] Beyond coagulopathies, hypothermia has been implicated in hypoxia, endothelial dysfunction, cell death, and multiorgan dysfunction.[18] Hypothermia is

considered one of the three components of the "Triad of Death" which also includes acidosis and coagulopathy.[14,16,19]

It has been theorized that uncontrolled hemorrhage alone (in the absence of other trauma) can lead to profound systemic inflammation. In a non-human primate study, Burdette et al found molecular markers indicating an inflammatory response following a surgical procedure.[20] These inflammatory processes may contribute to increased metabolic demand in these patients who are already experiencing a large sympathetic nervous system response and a baseline increase in metabolic requirements.[21]

Hemorrhage in trauma patients can lead to the loss of many ions in the blood, namely calcium which is an important component of platelet activation, extrinsic and intrinsic coagulation pathways, and cardiac contractility. Not only is there a decrease in the absolute volume of calcium available to the body, but there is also an increase in calcium utilization as platelets become activated and blood clotting occurs.[22] A decrease in calcium not only hinders coagulation but may also decrease cardiac output, as cardiac contractility is regulated by intracellular calcium concentrations. [23,24]

Perhaps the most imminent complication associated with traumatic injury is hypotension. Trauma patients can experience hypovolemic shock as a result of significant blood loss. As blood pressure decreases, patients may succumb to hemorrhagic shock.[25] An analysis of war-related mortality indicated that nearly 20% of casualties experienced hypotension as a result of traumatic injury.[26]

2.3 Fluid Resuscitation

Because of the imminent threat that hypotension presents to trauma patients, they will almost universally receive some form of IV fluid resuscitation. [27,28] At this time there

is significant debate regarding the most effective fluid for resuscitation following trauma. While several categories of fluid can be utilized for this application such as colloids and blood products the most common solutions in use are crystalloids such as normal saline or lactated ringer's (LR).[27] Even in instances of hemorrhagic shock, when treatment will ultimately require blood products, the initial fluid infused is still a crystalloid. The "best" crystalloid for IV fluid resuscitation in trauma patients is a topic of great contention and this study hopes to provide some clarity to that debate going forward.

A survey of state protocols from 2017 describes several state emergency medical services (EMS) protocols for fluid resuscitation of hypotensive trauma patients. Of the twenty-seven states with publicly available protocols, 15 states recommend normal saline as the fluid of choice with eleven states recommending the use of either normal saline or lactated ringers. One state recommended lactated ringers exclusively. Most states describe goal systolic blood pressures in the range of 80-100 mmHg.[29] The most important difference between normal saline and lactated ringer's is their classifications as unbalanced and balanced fluids respectively. Balanced crystalloids are closer in electrolyte and acid-base composition to blood plasma than normal saline which contains only sodium chloride.[30] The theorized benefits of balanced crystalloids over normal saline are numerous, however to this point there have been very few trials that have evaluated the efficacy of these solutions in trauma patients, and at this time, there have been no studies that have evaluated mortality as the primary outcome. A study by Young et al comparing the effects of Plasma-Lyte A (another commonly used balanced crystalloid) vs normal saline in regards to acid-base status and serum chloride levels of

trauma patients demonstrated significant benefit in the balanced crystalloid arm (95% CI of 1.6 to 6.7 for base excess and 95% CI of -10 to -3 chloride).[31]

In addition to balanced crystalloids, there is reason to believe that there could be a benefit from the use of solutions that contain bicarbonate in trauma patients. The specifics of these proposed benefits will be described in more detail below but suffice to say that as the most commonly utilized physiological buffer, bicarbonate can play a significant role in stabilizing physiological pH.[32] The specific bicarbonate-containing solution being proposed in this study is described in a paper by Hashemi et al. Rather than being purchased by a manufacturer, it is made by adding three, 50 mL vials of 8.4% sodium bicarbonate solution to 850 mL of 0.45% sodium chloride solution. [33] Beyond the proposed benefits of bicarbonate, this also yields a solution that is hyperosmolar compared to normal saline, a characteristic that is potentially beneficial in trauma patients. These benefits will be described in more detail later in this chapter.

2.4 Issues Associated with the Infusion of Normal Saline

Normal saline is easily the most commonly utilized fluid utilized in volume replacement in trauma patients.[27] It has long been used as the fluid of choice for EMS services and current state EMS guidelines generally favor the use of normal saline in trauma patients.[29] Despite its prevalence in the field of trauma medicine, the use of normal saline has been associated with significant complications which call into question its utility in this setting. [30]

As discussed previously, traumatic injuries often precipitate lactic acidosis as a result of poor tissue perfusion and this acidosis has wide-ranging physiological effects including coagulopathies. Perhaps the most frequently documented complication

associated with the infusion of large volumes of normal saline is hyperchloremic acidosis. [34-38] Contrary to conventional thought, this acidosis is not mediated through free proton in the normal saline solution itself. Despite having a pH as low as 4.6, the titratable acid in the solution is relatively small and is overcome quickly by physiological buffers.[39] Instead, the acidic effects of normal saline are mediated through other means, namely an increase in strong anion concentration and the dilution of physiological buffers.

The strong ion difference component of this acidosis is thought to develop through an increase in the concentration of strong anions, most notably chloride, as the concentration of chloride in normal saline is approximately 50% higher than blood plasma. [35] Due to the law of electroneutrality an increase in strong anion concentration is met with a concurrent increase in cation concentration, in this case, the dissociation of protons from plasma water. This causes a non-anion gap metabolic acidosis that is often compounded by the concurrent high anion gap acidosis that is generated through the previously discussed anaerobic cellular respiration generated following trauma. [36] A study by Lee et al found that hyperchloremia 48 hours after admission and delta chloride levels have been associated with mortality in trauma patients ($p < 0.001$).[40]

The other significant contribution that normal saline makes to the development of acidosis is the dilution of physiological buffers, namely bicarbonate. The infusion of normal saline reduces the relative bicarbonate concentration in the blood. As CO_2 levels are not influenced by blood volume, there will be an increase in carbonic acid formation (through respiration) relative to bicarbonate concentration, which will tend the physiological pH towards acidemia.[39] This phenomenon has been observed with as little

as one liter of normal saline having a deleterious effect on base deficit in trauma patients.[41] Meta-analysis has supported the claim that patients receiving balanced fluids have been shown to have a better acid-base profile and lower incidence of hyperchloremia than those receiving normal saline.[42]

As discussed earlier, the development of acidosis contributes to coagulopathies. The pathogenesis of coagulation disorders is even more pronounced in patients receiving normal saline. A study by Darlington et al in acidosis-induced pigs demonstrates a decrease in clot strength and a decrease in the rate of clot formation. [43] Campbell et al noted that both platelet-rich plasma and platelet-poor plasma that was acidified demonstrated reduced clotting time, and infusion with normal saline further exacerbated these clotting delays while also weakening clot strength.[44] The effects of normal saline on coagulation may extend beyond the effects of acidosis. The infusion of normal saline has been implicated in decreasing blood calcium levels and can even result in hypocalcemia.[45,46] As previously discussed, reductions in serum calcium levels can have deleterious effects on platelet activation, both intrinsic and extrinsic clotting cascades, and cardiac contractility. In patients that are already at risk for developing shock and hemorrhage, these effects should be considered.

Further weakening the resume for normal saline as the solution of choice in patients at risk for hemorrhage are its effects on the coagulation factors. In vitro models indicate that normal saline, even in the absence of hypothermia or acidic pH, reduces the rate of conversion of prothrombin to thrombin. [47] Infusion of crystalloids has also been associated with lower concentrations of albumin and fibrinogen while also decreasing hepatic albumin synthesis in swine models. [48] While detrimentally affecting important

components of the clotting cascade, crystalloid dilution does not appear to impair protein C activity in vivo, suggesting that while clotting activity may be compromised, the anticoagulative components of the plasma may maintain their full effect.[49] It should be noted that the effects noted in albumin, fibrinogen, and protein C were observed with both balanced and non-balanced crystalloid solutions.

In a study observing the effects of hemorrhagic shock on rats, among all the fluids tested for resuscitation (including hypertonic saline and lactated ringers) normal saline was the least effective at maintaining liver and kidney function and limiting muscle damage. [50] Several human studies have supported these claims, linking normal saline to more major adverse kidney events than compared to balanced crystalloid solutions (OR 0.82, 95% CI 0.70-0.95).[51] In addition to the potential end-organ damage associated with normal saline it may also influence medical management in the hyperacute setting. Studies observing fluid choice in patients undergoing major abdominal surgery found that patients receiving normal saline required significantly more vasopressor support than those receiving balanced solutions.[52]

There are several deficiencies associated with the use of normal saline in trauma patients. The potential exacerbation of electrolyte imbalance, acidemia, coagulopathies and several other complications cannot be understated in such a critically ill patient population such as those that suffer severe traumatic injuries. These concerns have caused some to recommend abandoning the use of normal saline, questioning whether its use may cause more harm than good. [53,54] While there appears to be a substantial amount of evidence undermining the efficacy of normal saline in the management of trauma patients, it likely has utility in other applications such as some surgical procedures, stable

ED patients, and the management of DKA (where LR may prolong the duration of hyperglycemia). [55-57]

2.5 Lactated Ringer's Solution

In patients that have experienced severe traumatic injuries, there is sufficient evidence to suggest that Lactated Ringer's may be an ideal candidate in many situations. There are, of course, instances where the use of Lactated Ringer's should be deferred in favor of another fluid. Both the proposed benefits and potential drawbacks will be discussed in this section.

As discussed previously, the development of acidosis secondary to the infusion of normal saline and normal physiological response to trauma can contribute to numerous complications in these patients. The acid-base benefits are not only linked to LR's more physiological chloride concertation but also its inclusion of the conjugate base lactate. Lactate plays several important roles that can reduce free proton concentration such as binding protons to act as a base directly, being utilized by cells as an energy source to decrease ischemia, or by being converted into bicarbonate after lactate dehydrogenase mediated conversion to pyruvate.[58] Several studies have now found that the same level of hyperchloremic acidosis that is associated with normal saline infusion is not associated with the infusion of LR. Ayebale et al found that patients receiving emergent C-sections (which may be thought of as analogous to trauma) had higher rates of acidosis when given normal saline compared to those given LR (RR 1.29, 95% CI 1.18-2.31). [59] Other studies looking at acid-base status following surgery or other settings where blood loss is expected (such as blood donation) support these findings, showing better levels of base excess in patients receiving balanced fluids compared to those receiving normal saline.[60-

[62] Several studies have found that patients experiencing various forms of metabolic acidosis, including those with sepsis, benefit from LR by decreasing mortality rates and improving acid-base status. [63-65] Similarly, in children with hypovolemia secondary to gastroenteritis, the use of LR was associated with the best levels of plasma bicarbonate when compared to other fluids including normal saline. [66]

While the effects of pH on coagulation have been discussed thoroughly, there have been multiple studies that have observed the benefits of LR on coagulation directly. Sawhney et al found that compared to normal saline, LR produced stronger clots and improved coagulation time in surgical patients.[67] While there have been very few studies that have examined the effects of coagulation in humans, there have been several studies that utilized hemorrhage in a swine model to observe the effects of various fluids on coagulation. These studies indicate a better resolution of normal coagulation, improved clot characteristics, and time to coagulation that is closer to physiological baseline in the pigs receiving LR.[68-70]

In addition to its effects on coagulation, balanced fluids have been associated with beneficial effects in several different organ systems. According to Roquilly et al balanced solutions may be better in patients with brain injury (although it should be noted that LR should not be considered in this group as it is physiologically hypotonic, potentially incurring mortality risk in patients with TBI) as a result of their metabolic profile.[71] In a study performed in rats it was observed that correcting pH can be beneficial to myocardial elastance and vascular responsiveness following hemorrhage.[72] Similarly, it was observed that LR can induce antiapoptotic effects in the hearts of traumatically injured rats, potentially improving recovery.[73] Balanced fluids have been linked to better

renal outcomes as well, including decreased incidence of acute kidney injury in rat models.[74] It has also been observed that the use of LR was effective at preventing mitochondrial damage in both the liver and kidneys in rats with hemorrhagic shock.[75] Gastrointestinal benefits may not be isolated to the liver, as LR has been shown to reduce myeloperoxidase (an enzyme that produces reactive oxygen species) levels in rats compared to normal saline.[76,77] Small studies have shown smaller volumes of LR may be required during resuscitation and that fluid accumulation was decreased in pediatric patients with septic shock.[78] Overall systemic inflammation may be attenuated by the administration of LR, as rats that experienced hemorrhagic shock were found to have a reduction of apoptosis through the blockade of the IGF II R pathway.[79] In addition to its anti-inflammatory effects, LR can also produce antioxidative compounds. In the cytosol, lactate is converted into pyruvate, a powerful antioxidant that may be able to counteract some of the free radicals that are generated by the metabolic derangements produced during trauma that are outlined above.[80]

LR is a very good choice for fluid infusion and offers significantly fewer complications than NS, and in many cases, balanced solutions should be considered before the administration of normal saline. [81] There are, however, situations where LR may be contraindicated. While LR can be converted into bicarbonate, it is important to note that LR infusion with exogenous bicarbonate is contraindicated as the calcium contained within the LR solution can produce calcium carbonate which may precipitate out of solution.[82] This reaction should be considered in patients where concurrent sodium bicarbonate administration is likely. Another potential complication associated with LR is hyponatremia, as the solution has a lower than physiological concertation of sodium.[83]

While we have established that in some cases lactate may be used as an energy source, studies in rats indicate that this benefit may be absent following traumatic brain injury. [84] Finally, and perhaps most importantly, the administration of LR is contraindicated in patients with a potential traumatic brain injury as it can increase mortality in these patients.[85] Following TBI, patients are at risk for the development of increased intracranial pressures (ICP). Hypotonic solutions such as LR can exacerbate increased ICP as the relatively high solute concentration within the cells draw in free water through osmotic gradients.[58] For these reasons, patients with suspected TBI will not be included in the LR arm of the study. They will be included in the bicarbonate solution arm as this solution will be hypertonic.

2.6 Bicarbonate Solution

The bicarbonate solution outlined previously is not commonly referred to in the literature despite being used commonly in surgical and emergency medical settings. The possible benefits of the solution stem from two key characteristics of the solution. The first proposed benefit is its relative hypertonic concentration. Using RxKinetics' method for calculating osmolarity, the solution would contain approximately 431 mOsm/L.[86] At this concentration, one liter of fluid contains as much solute as approximately 1.4 liters of normal saline. The benefits of hypertonic fluids are thought to be mediated by the mobilization of fluid in the extracellular and intracellular spaces into the vasculature, increasing intravascular volume, and improving perfusion.[87] The other key attribute of this solution is the inclusion of bicarbonate, a key physiological buffer that can help combat acidosis and aid in recovery.

The role of bicarbonate in acid-base balance is well established. Bicarbonate can react with free protons to generate compounds that can either be exhaled or excreted in the urine to maintain acid-base homeostasis.[88] Bicarbonate reabsorption is performed primarily in the kidneys where some acid excretion also occurs.[32] The supplementation of additional exogenous bicarbonate has been theorized to improve outcomes, however many studies have failed to demonstrate a mortality benefit. It is thought that the rapid administration of high concentrations of sodium bicarbonate can lead to the accumulation of carbon dioxide in the tissues leading to acidosis as the respiratory system is unable to clear the produced CO_2 as quickly as it is produced.[89] Therefore, it's reasonable to suspect that when given as an infusion, as is described in this study, we may be able to overcome the issue associated with pushing concentrated ampules of bicarbonate. A survey of clinicians in New Zealand and Australia indicated that the preferred administration of sodium bicarbonate in a study would be an infusion as opposed to a bolus of concentrated solution.[90] While the use of concentrated bicarbonate solutions in acidotic patients is controversial, the use of buffered crystalloids solutions has shown benefit.[62] The use of bicarbonate may be beneficial over lactate as a buffer as it does not require conversion into pyruvate and metabolism through glycolysis to generate the end product.[58] The composition of the proposed solution may also contribute to a decrease in the exacerbation of acidemia. A study by Joseph et al found that with increases in the concentration of chloride (5% NaCl vs 3% NaCl) there tends to be a decrease in pH in trauma patients.[91] The proposed solution contains only 65 mOsm/L of chloride which should help reduce the incidence of hyperchloremia.

The proposed bicarbonate solution may also be beneficial in the reduction of inflammation in trauma patients. While no studies have been performed that observe the effects of bicarbonate or hypertonic fluids on inflammation in trauma patients in general, many studies have been performed that induce some form of hypoxic distress that may be used as an analog for the physiological response to trauma. A study on patients undergoing surgical repair of femur fractures found that pre-operative hypertonic fluids may attenuate the effects of polymorphonuclear leukocyte activity thereby reducing inflammation. [92] Another study by Junger et al found that hypertonic fluids given in the prehospital setting to patients suffering from hypovolemic shock may reduce inflammation by reducing the expression of certain cell-surface markers on neutrophils leading to reduced degranulation.[93] In addition to attenuation of neutrophil function, hypertonic fluids have been shown to induce polymorphonuclear cell apoptosis in in vitro studies. [94] As discussed previously, a mediator of inflammation is a lack of end-organ perfusion. The use of hypertonic fluids (specifically in acutely alcohol-intoxicated patients) may be able to improve perfusion through the correction of arginine vasopressin (AVP) levels, indirectly increasing mean arterial blood pressure and potentially reversing end-organ hypoperfusion.[95] Bicarbonate itself may also help reverse hypoxic inflammation, as studies in athletes showed that bicarbonate was effective at reducing the incidence of arterial oxygen desaturation. [96] A similar study conducted on cyclists found that bicarbonate improved acid-base balance recovery in hypoxic conditions.[97]

As stated earlier, LR is a poor choice in patients with TBI due to its low osmolality. As a slightly hypertonic solution that contains bicarbonate, the solution proposed in this study could incur mortality benefits in these patients. Studies in canine

models indicate that hypertonic solutions prevent the formation of cerebral edema as hypertonic solutions mobilize free water out of cells.[98] In humans, hypertonic saline solutions were shown to reduce inflammation in trauma patients with TBI.[99] Mannitol is generally considered the first-line treatment for patients with elevated intracranial pressure (ICP), however, a meta-analysis by Mortazavi et al found that saline-based hypertonic solutions may be more efficacious in these patients.[100] The benefits of the solution may extend beyond the fact the solution is slightly hypertonic, as a study by Bourdeaux et al found that bicarbonate infusion over 30 minutes was more effective at reducing increased ICP than 5% NaCl solutions, indicating that bicarbonate itself may play a role in the reduction of ICP.[101]

Hypertonic solutions are also the preferred treatment for burn patients. One meta-analysis found that patients receiving hypertonic fluid required less volume.[102] A study in mice with severe burns indicated that hypertonic solutions reduced rates of pulmonary edema and hyponatremia and attenuated oxidative stress.[103] A study in rats also supports the finding that hypertonic solutions can protect against lung injuries following burns through the inhibition of inflammatory pathways. Hypertonic saline was also found to be beneficial to the kidneys of rats that were severely burned by reducing renal edema and reducing hyponatremia.[104] Studies have also shown reduced rates of intestinal edema in rats that experienced severe thermal injuries.[105]

End-organ benefits of the proposed solution may extend beyond burn patients. Certain surgical procedures such as endovascular aneurism repair are associated with acute kidney injury (AKI), however, the administration of bicarbonate and standard hydration has demonstrated protective effects when compared with adequate hydration

alone in these patients (95% CI of 0.05-0.89).[106] Trauma patients frequently receive iodinated contrast during computed tomography scans in the secondary survey which has long been considered a risk factor for AKI.[107] Patients that undergo percutaneous coronary interventions are also at risk for the development of AKI, and in this population hydration and bicarbonate are found to be effective strategies for limiting contrast-induced kidney injury.[108] Renal benefits of bicarbonate are also seen in patients with chronic kidney disease where it appears to incur a benefit on mortality and kidney function (Mortality RR adjusted 95% CI of 0.18-.074, 34% improvement in creatinine clearance, p-value <0.001) [109] Studies in rats with hemorrhagic shock that were resuscitated with blood and crystalloid had less kidney and liver damage when the fluid utilized was hypertonic.[50] One study also demonstrated less lung injury in hemorrhaged rats that received hypertonic solutions through the upregulation of aquaporin activity.[110] Vascular endothelial function was also improved in human patients with chronic kidney disease when metabolic acidosis was treated with sodium bicarbonate.[111]

Isotonic solutions (normal saline) are generally considered the first-line management for trauma patients and in the cases where other solutions are used, they are usually hypotonic (LR). Despite this convention, there have been multiple studies that indicate that hypertonic solutions are not only safe but may also be more beneficial than solutions with lower tonicity. A study by Han et al found that solutions as high as 3% hypertonic saline solution (which is over twice as osmolar as the proposed solution) were safe in patients with hypovolemic shock.[112] A meta-analysis of hypertonic solutions found that solutions as high as 7.5% NaCl (several times more concentrated than the proposed solution) do not increase mortality in trauma patients leading the authors of the

study to suggest that highly concentrated hypertonic solutions may be viable options for the resuscitation of trauma patients.[113] Another review by Ertmer et al took it a step farther stating that "… administration of hypertonic solutions may exert beneficial effects beyond hemodynamic stabilization," on trauma patients. There is sufficient evidence to suggest that the proposed bicarbonate solution is not only safe but possibly more effective than traditional solutions when used in the resuscitation of trauma patients.

2.7 Review of Confounding Variables

There are few factors that influence both the effects of intravenous fluid and mortality, and a review of the literature did not reveal any clear confounding variables. Some factors that should be considered include the amount of fluid given in the prehospital setting, length of transport which may prolong definitive care and exacerbate acidosis, pre-existing diseases that influence acid-base balance such as chronic kidney disease and COPD, current medications that can influence acid-base balance such as acetazolamide or oral bicarbonate, and liver dysfunction which could impair lactate metabolism.[114-117] Based on the design of the study as a randomized controlled trial with a large sample size, we expect to be able to control for both known and unknown confounding variables.

2.8 Review of Relevant Methodology

This study is novel in several ways. Firstly, this is the first study comparing different crystalloid solutions in trauma patients to utilize mortality as the primary outcome. Secondly, this is the first study that will randomize and initiate the intervention in the field. Thirdly, this is the first study that will compare the proposed bicarbonate solution to commercially available crystalloid solutions. Due to the unique parameters of

this study, there will be a unique methodology implemented in the design, however many of the strategies utilized in similar studies can be adapted to work in this setting.

2.8.1 Randomization, Inclusion and Exclusion Criteria, and Blinding

A study by Young et al published in 2014 is perhaps the closest in design to what is being proposed here. This small study randomized trauma patients to receive normal saline or Plasma-Lyte A. Randomization was performed using a computer-generated randomization sequence in a 1:1 ratio. Solutions were covered in opaque wrappers and labeled with "study isotonic fluids" and a lot number and expiration date. They then placed thirty masked 1-L bags in suitcases that were assigned to the patient as the only source of crystalloid IV fluid for a 24-hour period. These principles will be modified and utilized in this study which will be described in the next chapter. Inclusion criteria were based on the triage criteria for severe acute injury at UC-Davis Medical Center, a level 1 trauma center. These criteria included "penetrating injury to the neck, chest, abdomen, or pelvis; Glasgow Coma Scale scores less than 9 or deteriorating by 2 after injury; systolic blood pressure less than 90 mm Hg; pulseless, injured extremity; or need for endotracheal intubation." They also included patients that required transfusion, surgery, or interventional radiology within 60 minutes of arrival to the hospital. Exclusion criteria included patients younger than 18 years of age, pregnant patients without apparent traumatic injury, patients on dialysis, incarcerated patients, and patients expected to expire within 48 hours.[31] These will serve as the foundation for the exclusion and inclusion criteria in this study.

2.8.2 Statistical Significance and Power and Sample Size Calculation

In order to achieve adequate power and statistical significance, we will follow the same parameters as several other RCTs that use mortality as a primary outcome (in this case sepsis patients receiving care in the ICU). These studies generally utilize a power of 80% with an alpha of 0.05. [118] As this study looks to evaluate mortality in critically ill trauma patients, we will include only patients that are found to have an injury severity score (ISS) 16 or greater in our analysis. Shi et al have found that patients with ISS scores of 16 or greater have a mortality rate of 12.6%.[119] While there have not been any studies in trauma patients comparing mortality based on the choice of crystalloids, Raghunathan et al performed a retrospective cohort study in critically ill sepsis patients comparing normal saline to LR with in-hospital mortality as the primary outcome. They found a relative risk reduction of 14% (19.6% vs 22.8% mortality, RR of 0.86, 95% CI of 0.78 to 0.94) in the patients receiving LR compared to those receiving exclusively non-balanced solutions (primarily normal saline).[120] This expected mortality rate of 12.6% and a predicted relative risk reduction of 14% will be utilized to calculate our sample size. This will be discussed in the following chapter. We are expecting minimal to no loss to follow-up as the primary outcome is in-hospital mortality.

2.8.3 Informed Consent in Emergency Research

Obtaining informed consent is an important part of studies utilizing human subjects. Unfortunately, patients that are critically injured and incapacitated as a result of traumatic injury may be unable to provide informed consent. Despite this concern, research is still required to improve the management of trauma patients in order to understand the best possible interventions to implement in these individuals. To address this hurdle, the Federal Drug Administration (FDA) has developed a policy known as the

Exception from Informed Consent (EFIC). The EFIC allows for a study to be conducted when there is the potential for clear benefit from the experimental intervention, but patients are unable to provide informed consent before the initiation of the intervention, such as the administration of intravenous fluid to correct hemodynamic instability. In order to protect patient autonomy, the FDA requires the engagement of the population that may be receiving the intervention through "community consultation" prior to the implementation of a study using EFIC. While the definition of community consultation is not clearly described it may include focus groups hosted at community organizations (such as churches or recreational centers) within the community where the study will take place or interviews of patients at participating hospitals to describe the rationale of the intervention and gauge their interest in participating in the study.[121] A study by Dickert et al found that community consultation focus groups that were interactive tended to have higher percentages of participants to be in agreement with the EFIC protocol for their particular study. These participants had better knowledge of the study design and goals compared to participants that attended noninteractive consultations.[122] This should be considered when organizing community consultation events although the exact threshold of what constitutes sufficient community consultation will be at the discretion of the institutional review board. In accordance with the FDA's policy regarding EFIC, the findings of the study will be made publicly available.

2.9 Conclusion

The "ABCs" (airway, breathing, and circulation) represent the essential components of the management of trauma patients. Circulation is perhaps the most elusive and confounding arm of this trinity, as hemodynamic compromise can arise from

a myriad of causes. For this reason, the administration of IV fluids to trauma patients represents a tenet of trauma management as it can quickly address circulatory dysfunction. Unfortunately, it is becoming more and more evident that the solution most typically utilized for fluid resuscitation, may in fact be contributing to severe metabolic derangements in these patients. The use of normal saline has been directly and indirectly implicated in the development of metabolic acidosis, end-organ dysfunction, coagulopathy, and electrolyte disturbances. Any of these factors on their own could represent an increased mortality risk for patients that are already critically ill.

This constellation of complications, however, may not represent a necessary evil that has long been thought to come with the territory of fluid resuscitation. There is evidence to suggest that the use of crystalloid solutions that contain buffers such as bicarbonate or lactate, may be able to achieve the same goal of maintaining hemodynamic integrity without the downside of the metabolic consequences that are imposed by normal saline.

To definitively answer the question of whether the choice of fluid can influence mortality in this critically ill population, a randomized control trial with a large sample size will be utilized. The scale and design of the study will account for confounders and heterogeneity amongst each of the three arms of the study. Current literature supports the need for this study, as mortality has not yet been used as a primary outcome when comparing fluid types. Both lactated ringer's and the proposed sodium bicarbonate solution represent promising potential replacements for normal saline in trauma patients moving forward, each offering their own unique benefits. To carry out this study in a manner that is both highly ethical and scientifically rigorous, we will utilize the FDA's

protocols regarding the Exception from Informed Consent with interactive community engagement and consultation.

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Chapter 3: Methods

3.1 Study Design

We will perform a multi-centered, double-blind randomized controlled trial utilizing adult trauma centers and emergency medical services (EMS) in the state of Connecticut and New York City. Trauma patients will be randomized using computer-generated randomization to either the control (normal saline) or one of the two intervention arms: lactated ringer's (LR) or the sodium bicarbonate solution (SBS) described in chapter 2. Computer-generated randomization will include screening for patients with suspected traumatic brain injury (TBI) as LR may increase mortality in these patients.[1] Patients with suspected TBI will be randomized to either normal saline (NS) or the sodium bicarbonate solution. Administration of the assigned fluid will take place during EMS transport and initial stabilization in the emergency department. Trauma patients being admitted will have blinded fluids discontinued upon arrival at their respective floor, at which point the overseeing provider will determine which fluid their patient will receive if any.

3.2 Study Population, Setting, and Sampling

3.2.1 Setting

Trauma centers in Connecticut will include Hartford Hospital, St. Francis Hospital and Medical Center, and Yale-New Haven Hospital as well as smaller trauma centers throughout the state. The EMS company utilized will be American Medical Response (AMR) of Connecticut Inc, specifically crews capable of performing intravenous catheterization and administration of intravenous fluids. In New York, hospitals will include Elmhurst Hospital Center, Jacobi Medical Center, King's County

Hospital Center, and other lower volume level I trauma centers. EMS services will include those that transport trauma patients to the aforementioned trauma centers.

3.2.2 Population

The study population will include adults 18 and older that meet at least one of the following criteria following traumatic injury: GCS under 12, those that require intubation, those with a pulseless extremity, penetrating trauma to structures proximal to the elbow or knee including the chest, neck, or abdomen, systolic blood pressure under 90, MAP under 65 or diastolic blood pressure under 40, open fractures, and those that required surgery, interventional radiology, or blood products within two hours of arrival at the hospital. Patients will be excluded if they meet any of the following criteria: patients younger than 18 years of age, pregnant patients, patients on dialysis, incarcerated patients, and patients expected to expire within 48 hours.

Patients that meet the criteria for inclusion will be randomized to one of the three study arms, however, only patients that meet criteria and have an injury severity score (ISS) of 16 or greater, the cutoff for "severe trauma," will be included in the analysis for outcomes. It should be noted that a patient's specific ISS will not be known until a review of their medical record is performed following their discharge, as it is calculated retrospectively.

3.2.3 Sampling

We will utilize total population sampling. The population will be defined as trauma patients with an ISS score of 16 or greater, who meet any of the inclusion criteria and none of the exclusion criteria who are treated at trauma centers in Connecticut or New York City.

3.3 Data Collection, Blinding, and Analysis

3.3.1 Collection

Medical records of patients enrolled in the study will be examined by research staff that are blinded to the fluid that the subjects received. Patients will be assigned unique identification numbers in two separate databases. One database will identify the solution that the patient was randomized to, while the other will contain only the results of the medical record review. These data will be evaluated monthly to determine if there are significant unanticipated trends that would precipitate premature discontinuation of the trial.

3.3.2 Sample Size Calculation

Based on our review of the literature we estimate a mortality rate of 12.6% in the control arm of the study. Based on other studies comparing balanced crystalloids in critically ill patients we believe that it is reasonable to expect a 14% relative risk reduction in both experimental arms of the study. We will use a significance level of $p<.05$ with a power of 0.80. Based on these proportions ($P_1 = 10.8\%$) we calculate that the study will require 5,004 patients per arm of the study for a total enrollment of 15,012 patients. Screenshots of the data input into the calculator will be available in Appendix B.

3.3.3 Blinding of Fluids and Assignment of Intervention

Fluids will be blinded to the participants and investigators using opaque wrappers indicating their expiration date, lot number, and their designation as “study IV fluid”. Fluids will be kept in one of two plastic bins (A and B). Bin A will contain all three fluids, divided into three sections (1A, 2A, and 3A). Bin B will contain only normal saline and the sodium bicarbonate solution, divided into two sections (1B and 2B). Patients with suspected TBI will be randomized to receive fluids from bin “B”. All other

trauma patients that meet the criteria will be randomized to receive fluid from bin "A". The contents of each respective bin will be rotated daily. The contents of each bin will be blinded to EMS and hospital staff, but each bin will be standardized across systems based on a written schedule. *Table 1* is an example of what a daily randomization schedule may look like over the course of a 3-day period.

Table 1. Randomization of study fluids in respective bins

Date	1A	2A	3A	1B	2B
06/01/2022	LR	NS	SBS	SBS	NS
06/02/2022	NS	LR	SBS	SBS	NS
06/03/2022	SBS	LR	NS	NS	SBS

Randomization of the patients to their respective study arms will be conducted in the field when subjects are determined to meet inclusion criteria. EMS staff will be able to utilize a mobile phone application or website that will randomly assign the subject to the control arm or one of the experimental arms. The randomization program will prompt EMS providers to acknowledge if there is suspicion of a TBI. If there is no suspicion of TBI then the patient will be randomized to a solution in the "A" bin. In the case that there is a concern for TBI the program will randomize the patient to one of the two fluids in the "B" bin.

3.3.4 Blinding of Outcomes

Members of the research team that are responsible for analyzing the primary and secondary outcomes of the study will be blinded to the fluid that the subjects receive. They will be provided with de-identified patient medical records and will be asked to collect data regarding mortality, time to discharge (when applicable), time to extubation (when applicable), the need for blood products within 24 hours, and ISS.

3.3.5 Adherence and Follow Up

The outcomes of interest of this study are generally thoroughly documented in the medical record and should be easily accounted for during hospitalization. Administration of the intervention will occur within minutes to hours of initial injury under the supervision of EMS and ED providers. For this reason, we do not expect any issues with adherence or follow-up.

3.3.6 Study Variables and Measures

The independent variable in this study will be the fluid that subjects are randomized to (NS, LR, or SBS), this will be recorded by EMS providers in the field. SBS and LR will be considered the intervention arms of this study. Dependent variables will include in-hospital mortality (primary outcome), need for intubation, duration of intubation (in days), need for blood products, and hospital stay (in days). These outcomes will be measured following discharge by research staff following a review of the medical record. These data will be gathered using the form in Appendix C. At this time, we have not identified any known confounders, and the study design should account for unknown confounding variables.

3.3.7 Analysis

The primary outcome of mortality will be analyzed using chi-square analysis. Secondary outcomes of time to extubation and time to discharge will be analyzed using Cox proportional hazards regressions. The other secondary outcome, the need for blood products, will be analyzed using chi-square analysis. While this study is designed to be large enough to control for confounding effects, descriptive statistics will be collected from medical record review to identify any factors that may influence outcomes outside of the intervention. These descriptive statistics will include age, BMI, sex, transport time,

comorbidities, initial GCS, total IV fluid volume administered, and ISS. Analysis will follow the intention to treat principle although it should be noted that based on the close supervision associated with the design of the study it is unlikely that there would be different results from per-protocol analysis.

3.3.8 Timeline and Resources

The study period will last 21 months unless the sample size is met earlier. Based on the data available from the state of Connecticut from 2000-2004 and 2008-2013 it is reasonable to expect more than 20,000 injury-related admissions and/or deaths per year.[2,3] Publicly available data from New York City from 2010-2013 demonstrates that there are on average approximately an additional 2,240 patients a year that meet inclusion criteria based on ISS (likely substantially more than that that did not have ISS recorded)[4]. Based on those data the full 21-month trial period may not be required. The study will begin in April of 2022 and run through December of 2023 unless adequate sample size is met before that point, with three months between January and March of 2022 reserved for community consultation (discussed below).

A study of this scale will be a significant undertaking. A small office will be required for the research staff to analyze data. Warehouse space will be required for the preparation of bins with appropriately randomized fluids. A distribution network will need to be in place to deliver appropriately blinded bins to EMS stations and hospitals as necessary. EMS providers will need to be trained on randomization and data collection. A pharmacist may be required to oversee the preparation of the SBS mixture. The sodium bicarbonate solution is not available commercially and will need to be made by adding 150 mL of 8.4% sodium bicarbonate to 850 mL of 0.45% NaCl to reach a final

concentration of approximately 1.3%. A program will need to be written or adapted for ease of randomization in the field. Software will be required to de-identify patient information and perform statistical analysis while maintaining HIPAA standards regarding confidentiality. Fluids and bicarbonate solutions will need to be sourced from the manufacturer.

3.4 Ethical Approval

3.4.1 Subject Protection and Confidentiality and the Exception from Informed Consent

Prior to the initiation of the study, we will receive approval from the institutional review board (IRB) of Yale University and the appropriate review boards associated with participating hospitals. The application to the committee will include the necessary documentation as outlined in the IRB guidelines titled "100 PR.1 Review by a Convened Institutional Review Board (IRB)". These guidelines outline the documentation required for approval by the IRB, including but not limited to: application, recruitment plan, proper health insurance portability and accountability act (HIPAA) documentation, and protocols. Additionally, a clear consent form that includes potential risks to subjects will be provided. This form can be found in Appendix A.

Obtaining consent will not always be feasible in the population, as some patients will be incapacitated as a result of their traumatic injuries. For this reason, the study will utilize the Food and Drug Administration's (FDA) Exception from Informed Consent (EFIC). Yale University's guidelines for EFIC are outlined in IRB documents titled "200 PR.2 Exception from Informed Consent Research." The document outlines nine factors that are required for IRB approval; 1. Concurrence by an Independent Physician, 2. Life-Threatening Situation, 3. Informed Consent Not Feasible, 4. Prospect of Direct Benefit, 5.

Research Impracticable in Absence of Waiver of Informed Consent, 6. Therapeutic Window, 7. Plan to Contact Legally Authorized Representative/Surrogate, 8. Informed Consent Procedures and Documents, and 9. Additional Protections (including community consultations and the establishment of an independent data monitoring committee to exercise oversight of the research and proper public disclosures).

In order to meet the requirements for community consultations, we will hold interactive open forums in the cities surrounding the state of Connecticut and in New York City. Forums in Connecticut will be primarily focusing on New Haven and Hartford Counties. Forums in New York City will be carried out in areas near participating hospitals. These sessions will be made available at community sites such as recreation centers, hospitals, and community centers throughout Connecticut and New York City. There will be five open forums in New York and an additional five in Connecticut with three of the five being held in New Haven or Hartford county. At least one forum will be held in Fairfield county, to include patients that may receive care at Bridgeport or St. Vincent's Hospital. These sessions will be heavily advertised throughout the community and participation will be encouraged by community members. Surrounding communities will be encouraged to attend as well. We will describe the goals of the study along with supporting rationale and potential risks. The forum will give community members an opportunity to ask questions and participate in the discussion. In accordance with the FDA's guidelines regarding EFIC, we will also hold public community sessions following the completion of the trial in order to share the results of the study.

All patients that meet study criteria will be opted in by default. For those that are not able to provide consent, a legally authorized representative (LAR) will be informed

and will be given the opportunity to opt the patient out of the study if they wish to do so. Patients that have the ability to make their own medical decisions will be able to opt-out at any time. Patient information will be de-identified and stored on encrypted servers that meet standards as described in HIPAA. Patients will be given documentation outlining their rights under HIPAA before obtaining consent by patients or their LAR. HIPAA protocols will be followed by the research team. Patient information such as outcome and treatment arm will only be available to research staff responsible for gathering data within the medical record.

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Chapter 4: Conclusions

4.1 Advantages and Disadvantages

As with any study, the study proposed above has its own strengths and weaknesses. Strengths of the study include its external validity, the practicality of the intervention, and study design and sample size. Weaknesses include the need for a large number of resources, complexity with coordination and implementation, and the limited number of fluids being compared.

The study was designed to have extremely high levels of external validity, as the goal of this research is to identify the benefit of certain buffered solutions in all trauma patients. Because nearly all trauma patients can be included in this study with relatively broad inclusion criteria, we would expect to enroll patients with several different mechanisms of injury as well as varying degrees of injury severity. In addition to the generalizability of the study, one of the major strengths of the intervention is its overall cost-effectiveness. All proposed study fluids are commonly used and relatively cost-effective. If the intervention is shown to be beneficial then it is unlikely that there would be significant hurdles in implementing a new solution as the standard of care nationwide. Finally, the study's design as a randomized controlled trial at multiple hospitals with a large number of patients will allow us to control for unforeseen confounders while also helping to identify any potential benefit that may be incurred by the intervention.

While the study was designed to limit disadvantages as much as possible, there are inherent challenges associated with designing a study of this scale. Perhaps the most notable of these challenges is the sheer number of resources that will be required to carry out this study. As this is a large multi-centered trial there will be challenges associated

with distribution to sites while maintaining appropriate blinding. We will require a large staff for intervention logistics, community consultation for the Food and Drug Administration's (FDA) Exception for Informed Consent (EFIC), and data monitoring and statistical analysis. In addition to these resources, there will be challenges associated with coordination and implementation. EMS crews will need to be trained on randomization of the intervention and proper documentation, sites will need to remain consistent with the bin blinding protocols, data will have to be collected from multiple sites, and there must be coordination between hospital and EMS crews to maintain continuity of the intervention. Finally, this study is only designed to evaluate two buffered fluids compared to normal saline. There are a number of strong candidates for IV fluid resuscitation that may be safer and more effective than normal saline, such as Plasma-Lyte or colloids. Unfortunately, it simply isn't practical in a study this large to include more than a few solutions. Perhaps at some time in the future, this study design could be adapted to evaluate other solutions.

4.2 Clinical Significance

Trauma is the leading cause of death in children and young adults.[1] Some of the deaths associated with trauma are unfortunately unavoidable, such as those that occur immediately following a traumatic event, however, there are a significant proportion of deaths that occur following initial stabilization in the ED.[2] It is unclear how many of these deaths are a direct result of metabolic derangements such as metabolic acidosis, but there is sufficient evidence to suggest that the metabolic effects imposed by normal saline may detrimentally contribute to certain homeostatic functions such as pH balance and hemostasis which can indirectly contribute to mortality.[3] These physiological effects are

thought to be the result of the composition of normal saline as a solution and they can potentially be mitigated through the use of buffered solutions that have more favorable metabolic profiles.[4]

The alternative solutions proposed in this study are widely used and are generally quite safe and cost-effective. By adding buffers such as lactate or bicarbonate, we hope to reduce some of the dilution of intrinsic buffers that occurs with normal saline, and the lower concentration of chloride as the primary anion may help reduce some of the strong ion effects that are also believed to contribute to acidosis. These solutions are quite inexpensive and offer volume expansion to maintain hemodynamic stability while hopefully reducing the metabolic effects associated with normal saline.

These proposed interventions could quite possibly change the standard of care for trauma patients. As trauma is such a common cause of mortality, the ramifications of this study could be enormous. While it is certainly possible that we may not see a significant change in overall mortality in these patients, the prospect of a cheap and effective therapy that has the potential to save countless lives is well worth it to attempt a study of this scale, as daunting as it may seem.

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Appendix A: COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

YALE UNIVERSITY

YALE UNIVERSITY SCHOOL OF MEDICINE

YALE-NEW HAVEN HOSPITAL

Study Title: Back to Basics: The Effects of Buffered Crystalloids on Mortality in the Setting of Severe Trauma

Principal Investigator: *Adrian Maung MD*

Co-Investigator: D. Seth Murphy PA-SII

Research Study Summary:

- We are asking you to join a research study.
- The purpose of this research study is to investigate whether intravenous (IV) fluid solutions that contain lactate or bicarbonate will reduce mortality in patients that suffer from severe physical trauma.
- Study procedures will include: **Patients that suffer from extreme trauma generally receive IV fluids to help maintain their blood pressure. In this study, we will randomize the contents of the fluids that patients receive.**
- **0** visits are required outside of the initial hospitalization.
- There are some risks from participating in this study. **Risks of the study include fever, pain, infection at the IV site, blood clots in the vein, cramps, and irritability.**
- The study may have no benefits to you. **This study may help reduce the risk of mortality for patients that suffer severe physical trauma.**
- There are other choices available to you outside of this research. **If you choose not to participate in the study, you may still require IV fluids following trauma, as this is a standard of care. The difference is that the fluid you receive will be selected by your provider.**
- Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.
- If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do

not understand. Once you understand the study, we will ask you if you wish to participate; if so, you will have to sign this form.

Why is this study being offered to me?

We are asking you to take part in a research study because **You have met our study criteria for patients that suffer from severe physical trauma**. We are looking for **15,012** participants to be part of this research study.

Who is paying for the study?

N/A

Will I be paid for this study?

Study participants will not receive financial compensation.

Who is providing other support for the study?

Yale School of Medicine

What is the study about?

The purpose of this study is to evaluate whether the use of fluids that contain bicarbonate or lactate can reduce mortality rates in patients that suffer from severe physical trauma.

What are you asking me to do and how long will it take?

If you agree to take part in this study, this is what will happen: This study will not require any additional work from you, the study participant. If you participate in this study you will receive intravenous (IV) fluid as you normally would to help maintain your blood pressure. The fluid that you receive will be randomly selected by a computer, much like pulling a name out of a virtual hat. Participants will receive one of three different types of fluids. Some patients will receive "Normal Saline" (0.9% sodium chloride). Other patients will receive solutions with "buffers". These solutions are Lactated Ringer's solution or 0.45% sodium chloride with sodium bicarbonate. The buffers in these solutions are lactate and bicarbonate respectively. Buffers are solutions that help maintain acid-base balance.

After participants receive these fluids in the ambulance and the emergency room, the remainder of their hospital stay will proceed as it normally would. We will collect data from the participant's medical records including whether the participant survived their hospital stay, how long the patient was in the hospital, if the patient required blood, if the patient needed a breathing tube (intubation), and how long the patient required the breathing tube.

Results of our study will be made publicly available.

What are the risks and discomforts of participating?

The most common foreseeable risk of the study is pain or discomfort at the IV site. All of the medications and fluids in this study are generally well tolerated. Rare risks include shortness of breath, infection at the IV site, and blood clots at the IV site. These can be managed in the hospital during your admission at the discretion of your provider but may require supplemental oxygen, antibiotics, and anticoagulants (medication to resolve blood clots) respectively. Patients that receive bicarbonate may experience irritability.

How will I know about new risks or important information about the study?

We will tell you if we learn any new information that could change your mind about taking part in this study.

Results of this study will be made publicly available when it has been compiled and evaluated.

How can the study possibly benefit me?

We suspect that the intervention arms of this study (either of the fluids that contain buffers) may reasonably reduce the rate of mortality in patients that suffer from severe trauma. It is possible that you may have improved outcomes if you are randomized to one of these intervention arms.

How can the study possibly benefit other people?

In the future, this study may influence the way that trauma patients are treated with IV fluids. If findings are statistically significant this study could drastically improve the outcomes of trauma patients going forward.

Are there any costs to participation?

If you take part in this study, you will not have to pay for any services, supplies, study procedures, or care that are provided for this research only (they are NOT part of your routine medical care). However, there may be additional costs to you for medical costs that are not related to your IV fluids.

Instead of participating in this study, you have some other choices.

You could:

- Get treatment without being in a study. **This would most likely include receiving normal saline, which is one of the fluids included in this study. This determination would ultimately be made by your provider in the ambulance or hospital.**

How will you keep my data safe and private?

We will keep the information we collect about you confidential. We will share it with others if you agree to it or when we have to do it because U.S. or State law requires it.

For example, we will tell somebody if we learn that you are hurting a child or an older person.

Information will be stored in encrypted and password protected in secure servers.

When we publish the results of the research or talk about it at conferences, we will not use your name. If we want to use your name, we would ask you for your permission.

We will also share information about you with other researchers for future research but we will not use your name or other identifiers. We will not ask you for any additional permission.

We will not be collecting or storing any specimens from this study.

What information will you collect about me in this study?

The information we are asking to use and share is called "Protected Health Information." It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.

The specific information about you and your health that we will collect, use, and share includes:

- Research study records
- Medical and laboratory records of only those services provided in connection with this Study.
- The entire research record and any medical records held by ***participating hospitals*** created from: ***The date of your hospital admission*** to: ***your discharge date***
- Records about phone calls made as part of this research
- Records about your study visits
- Information obtained during this research regarding
    - Whether you survived your hospitalization
    - Medical records describing the severity of your injuries
    - Whether or not you required blood transfusion
    - Basic blood cell counts and complete metabolic panels to monitor for adverse events
    - Whether you required a breathing tube and how long it was in place
    - When you were discharged from the hospital

How will you use and share my information?

We will use your information to conduct the study described in this consent form.
We may share your information with:

- The U.S. Department of Health and Human Services (DHHS) agencies

- Representatives from Yale University, the Yale Human Research Protection Program and the Institutional Review Board (the committee that reviews, approves, and monitors research on human participants), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- The U.S. Food and Drug Administration (FDA) This is done so that the FDA can review information about ***the IV fluids*** involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- Drug regulatory agencies in other countries
- Health care providers who provide services to you in connection with this study
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Principal Investigator of the study
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

Why must I sign this document?

By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

However, this is a double-blinded treatment study and if you sign this permission form, you will not be allowed to look at or copy your study-related information until after the research is completed.

What if I change my mind?

The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by telling the study staff or by writing to ***Dr. Adrian Maung*** at the Yale University, New Haven, CT 06520.

If you withdraw your permission, you will not be able to stay in this study but the care you get from your doctor outside this study will not change. No new health information identifying you will be gathered after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to ensure the integrity of the study and/or study oversight.

What if I want to refuse or end participation before the study is over?

Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment. Not participating or withdrawing later will not harm your relationship with your own doctors or with this institution.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.

The researchers may withdraw you from participating in the research if necessary. **You may be withdrawn from the study, for example, if you experience an unforeseen complication.**

What will happen with my data if I stop participating?

If you choose to withdraw from the study, data that has already been collected may still be used in the study, however, no new data will be collected.

Who should I contact if I have questions?

Please feel free to ask about anything you don't understand.

If you have questions later or if you have a research-related problem, you can call the Principal Investigator at (203) 432-4771

If you have questions about your rights as a research participant, or you have complaints about this research, you call the Yale Institutional Review Boards at (203) 785-4688 or email hrpp@yale.edu.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

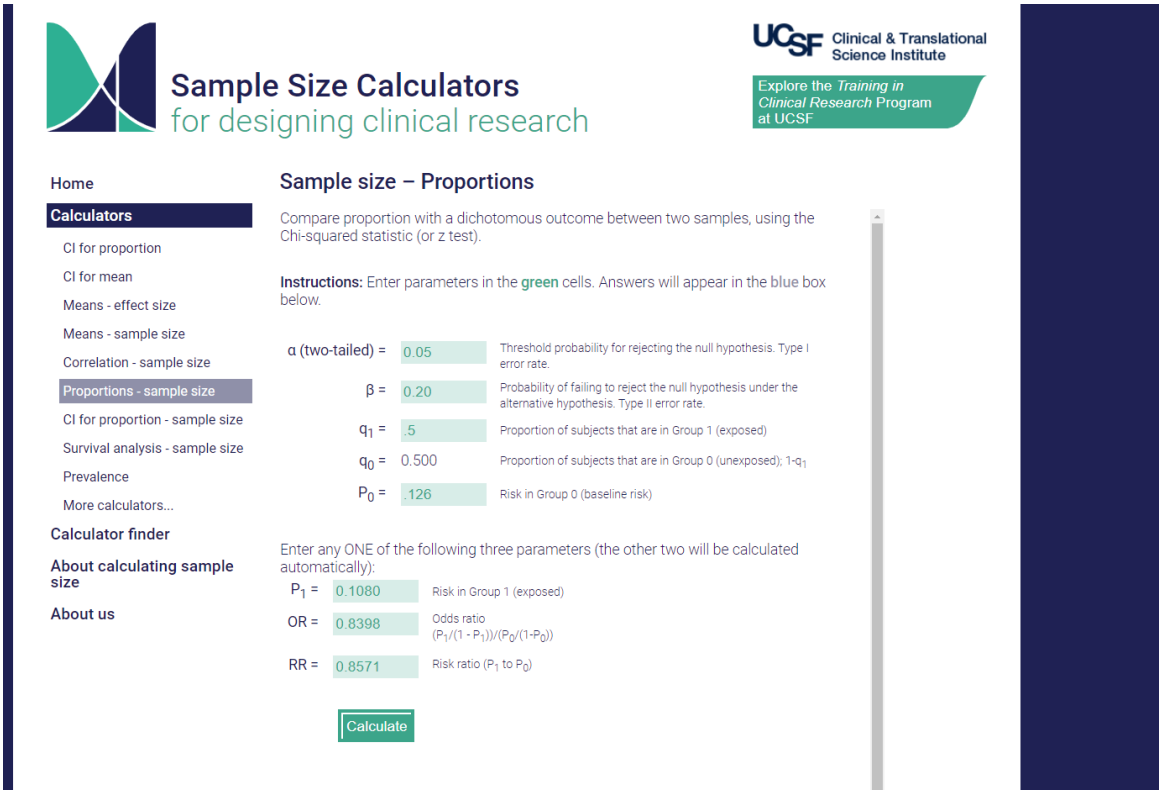
Authorization and Permission

Your signature below indicates that you have read this consent document and that you agree to be in this study.

We will give you a copy of this form.

Participant Printed Name	Participant Signature	Date
Printed Name of Legally Authorized Representative (if the participant is unable to consent)	Signature of Legally Authorized Representative	Date
Person Obtaining Consent Printed Name	Person Obtaining Consent Signature	Date

Appendix B: Sample Size Calculations



Sample size (without continuity correction)

	N	Outcome+	Outcome-
Group 1:	5004	540	4464
Group 0:	5004	631	4373
Total:	10008	1171	8837

Appendix C: Clinical Trial Participant Data

To be initiated by EMS staff and given to documenting trauma RN

EMS Staff

- Fluid Bin (Circle one) A/B Fluid Number (Circle one) 1/2/3
- Date _____
- Transport Time _____
- Initial GCS _____
- Fluid Volume given by EMS (in mL) _____

Documenting Trauma RN

- Patient MRN _____
- Fluid Volume given in ED **ONLY _____**

Research Assistant

- Patient Age _____
- Patient Sex _____
- Patient BMI _____
- Injury Severity Score (ISS) _____
- Comorbidities
    - Diabetes
    - Hypertension
    - Coagulopathy (specify if known) _____
    - CAD
    - Other heart disease (specify) _____
- Did patient survive to discharge? (Yes/No)
- Did patient require intubation? (Yes/No)
- If yes, how long was the patient intubated (in days) ____
- Did the patient require blood products? (Yes/No)

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